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Violet Is Not Always Beautiful

IODINE and the thyroid gland have been inextricably linked since the discovery of the former during the French military expansion of the early 19th century. Napoleon's ambitions had set France at war with almost all her neighbors simultaneously. Blockaded at sea by the British navy and on land by the armies of Prussia and Austria, France found that the supply of chemicals necessary for the manufacture of gunpowder was cut off. The Emperor set his scientists to manufacture saltpeter artificially in special "nitre plantations." One of the steps involved extracting soda from ashes of seaweed in large metal vats. The vats were cleaned periodically with hot acid. Observing this process one day in 1811, Bernard Courtois was astonished to see, arising from the muck, intensely beautiful violet-colored vapors which deposited lustrous metal-like crystals on the cooler parts of the vessel. Samples were sent to the distinguished French chemist Gay-Lussac, who named the material *iode,* derived from the Greek word meaning violet colored. Some of this material came immediately into the enemy hands of Sir Humprey Davy, who proved that it was an element and anglicized its name to iodine.

Eight years after Courtois' discovery, Andrew Fyfe, a lecturer in chemistry at the University of Edinburgh, found that common sea sponges also contained large quantities of iodine. Shortly thereafter, Jean-François Coindet, a prominent Swiss physician who commonly treated his many goitrous patients in Geneva with the centuries-old remedies of burnt sponge or seaweed, suspected that the violet crystals might be the active ingredient common to these two substances. He reported the great success of his therapeutic trial of the new element in 1820 and the use of iodine rapidly spread throughout the Western world, much as cortisone did more than a century later. This new miracle substance was prescribed for every conceivable condition ranging from chilblains and dropsy through scrofula and syphilis. From the initial publication of tincture of iodine in an 1821 pharmacopoeia by François Magendie, 1,700 approved names of iodine-containing substances were listed by 1956.

Since burnt sponge and seaweed had been administered topically as well as taken orally, the methods of applying iodine during the 19th century were scarcely less numerous than the variety of preparations available. It was given as a vapor, in baths, in pills, in candy, by irrigation, in cigarettes, in soaps, in hair tonics, and as a contraceptive. In French hospitals it was common practice to hang strips of gauze saturated with iodoform from the ceiling like flypaper. Even the laity were so impressed with this new gift from the collaboration of Science and Heaven that they carried little bottles of iodine hung round their necks like amulets to ward off disease. In Geneva it was said that the iodine dropping-bottle replaced the bonbonniere as the centerpiece of social gatherings in the evening salons.

The first specific reference to the use of tincture of iodine in wounds was by the English surgeon John Davies in 1839. It was widely used in the treatment of battle injuries during the American Civil War and World War I, but rapidly lost favor as a first line of antibacterial defense when the more efficacious and less necrotizing antibiotics came on the scene during World War II. Nevertheless, it is still widely employed for its antibacterial properties.

Iodine and the Thyroid Gland

Getting back to the relation of iodine to the thyroid gland, at the time Coindet initiated his therapeutic trial, the fact that the thyroid contained iodine was as unknown as was the purpose for which God set this strange organ in the neck. In spite of this ignorance, a number of important studies and theories appeared during the 19th century. In 1831 Jean-Baptiste Boussingault, a mining engineer with protean talents, discovered during a sojourn in Colombia—a region with unevenly distributed severe endemic goiter—that the natives who used salt from certain natural deposits had less goiter than those taking salt from elsewhere. He found that the iodine content of the salt used by the different groups was in-

versely correlated with the prevalence of thyroid enlargement and suggested that providing iodized salt would be a useful prophylactic measure against goiter. During the mid-19th century another French chemist, Gaspard Adolphe Chatin, found that there was a general deficiency of iodine in the water, soil and vegetables in areas with a high incidence of goiter.

However, the French Connection was not widely accepted. Iodine was often given in excessive doses and produced serious reactions in some persons. Its use in the treatment of many diseases, including goiter, was therefore gradually abandoned. In fact, in 1821, one year after his initial earthshaking discovery, Coindet warned that in certain goitrous patients treated with iodine, toxic symptoms including accelerated pulse, palpitation, increased appetite, rapid emaciation, insomnia and muscular weakness developed. He was the first, therefore, to describe thyrotoxicosis, several years before the publications of Graves or Basedow. It has even been suggested that the appropriate eponymic designation of spontaneous hyperthyroidism should be "non-iodide-induced Coindet's disease." Vagenakis and co-workers have recently shown that Coindet disease can also be induced by administration of large doses of iodide to patients with nontoxic goiter living in iodine-sufficient regions.

Toward the end of the 19th century, basic and clinical studies established that the thyroid contained a substance whose absence resulted in myxedema. Shortly after the discovery that orally administered thyroid substance was effective in treating myxedema it was found that ingestion of thyroid also caused a remarkable diminution in the size of nontoxic goiters. It was an attempt to find the active principle in the thyroid gland that caused goiters to shrink, not to identify the principle that was effective in treating myxedema (since myxedema was a much less common disorder than goiter), that eventually led German pharmaceutical chemist Eugen Baumann to the discovery in 1895 that iodine is an invariable constituent of the normal thyroid gland.

During the 20th century knowledge of the importance of iodine to thyroid physiology and disease has become increasingly sophisticated, albeit incomplete. David Marine revitalized the iodine-deficiency theory of endemic goiter and persuaded the school board of Akron, Ohio, to institute the first large-scale clinical trial to prove the efficacy of iodine-supplementation in preventing endemic goiter in children in 1917. Shortly thereafter, Plummer began preventing postthyroidectomy storm in thyrotoxicosis by preoperative treatment with Lugol's solution. Isolation of thyroxine by Kendall was followed by determination of its structure by Harington. The considerably more potent triiodothyronine was identified by Gross and Pitt-Rivers in both the thyroid and plasma in 1952. The extrathyroidal conversion of thyroxine to triiodothyronine and the intricate metabolism of thyroid hormones are currently under active investigation in a number of laboratories.

Hypothyroidism

Isolated reports of hypothyroidism induced by iodide therapy were followed by the demonstration by Wolff and Chaikoff in 1948 that administration of large doses of iodide to rats would transiently inhibit thyroid hormone formation for one to two days, although the inhibitory effect of iodide disappeared thereafter despite maintenance of high plasma levels of inorganic iodide. Raben proved that the Wolff-Chaikoff effect was due to a high intrathyroidal concentration of inorganic iodide; Braverman and Ingbar subsequently found that dissipation of the Wolff-Chaikoff effect was correlated with a decrease in the capacity of the thyroid iodide pump to maintain a high thyroid/plasma iodide gradient. This adaptive decrease in iodide pump activity to high concentrations of plasma iodide provided a plausible explanation for the infrequency with which iodide-induced myxedema or goiter is seen in spite of the widespread use of large doses of iodide in the treatment of chronic pulmonary and other diseases. Apparently, only patients with inherited autoregulatory defects or those with thyroids damaged by disease or surgical procedures (chronic thyroiditis, subtotal thyroidectomy, radioiodine therapy and the like) have this adaptation deficiency. The amelioration of thyrotoxicosis by large doses of iodide is not due to the Wolff-Chaikoff effect, but is due to a separate, poorly understood, action of high concentrations of intrathyroidal iodide to reduce thyroid secretion in very active glands.

The case reported by Prager and Gardner in this issue of the journal of an unusual occurrence of goitrous hypothyroidism apparently due to topical absorption of iodine chronically applied to a perineal fistula points out the ability of iodine to be absorbed from portions of the body other than the gastrointestinal tract and that organic,

as well as inorganic, iodine can produce the Wolff-Chaikoff effect after metabolic deiodination. Unfortunately, the possibility that their patient may have had chronic lymphocytic thyroiditis or some other non-iodide-related form of goitrous hypothyroidism is not excluded with certainty. The plasma inorganic iodide level obtained at a time when the patient was still being treated with iodine packing (although measured after storage for several months) was only three times greater than normal. The prompt regression of the patient's goiter with thyroxine therapy and the absence of antithyroglobulin and antithyroid microsomal antibodies do not exclude a diagnosis of chronic lymphocytic thyroiditis, contrary to the suggestion of the authors. Hypothyroidism from chronic thyroiditis is not always permanent and a spontaneous return to euthyroidism or even progression to thyrotoxicosis has occasionally been reported. More convincing validation would have been to show that readministration of high doses of iodide (either orally or topically) would produce a long-lasting block in thyroid hormone formation, but such confirmation would not be obtained easily.

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Natural Salicylate Foods

I DO THINK that we have underestimated the use of various kinds of foods for specific things. There are an awful lot of people who take large amounts of aspirin . . . much to the distress of their stomach linings. There are a whole host of [high-content] salicylate foods, and among these are potatoes, most of the fruits, apricots, almonds. . . . By utilizing some of these, one can reduce the need for exogenous medications. If you take four almonds, it will have enough salicylate for one 5-gram aspirin tablet. There are some of these nutritional applications that we have not utilized.

—IVAN E. DANHOF, MD, *Dallas*

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